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How many genes are part of the oscillatory network regulating somitogenesis? Developmental analysis and mathematical modeling of genes identified in functional genomic screens

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During somitogenesis, the formation of mesodermal segments is regulated by spatiotemporal oscillations of genes in the Notch, Wnt, and Fgf signaling pathways. These oscillations can range from cycling, or caudal to rostral shifts in expression, to stationary changes in expression level. Previously, we have used functional genomic analysis of cell culture models and Notch pathway mutants to identify genes that may potentially play a role in somitogenesis (William et al., Dev Biol, 2007; Loomes et al., Dev Dyn, 2007; Sewell et al., Dev Biol, 2009). This analysis has identified known cycling genes such as Nrarp, as well as novel descriptions of genes with other oscillatory expression patterns (Maml3, Nkd2) and genes localized to the paraxial mesoderm. This group includes Tcf7l2, Glcci1, Limch1, Rhpn2, A130022J15Rik, and 5 additional candidates that are currently being characterized. Understanding the regulatory network of these somitogenesis genes requires a systems-based approach, and we have developed mathematical model, based on empirical data from genetic studies, to generate predictions that can be validated in vitro. Altogether, we aim to identify the key regulatory steps in the complex oscillatory network regulating somitogenesis. Research supported by NIH RO1 AR050687.

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Zebrafish Nicastrin is required for mid- and hindbrain development

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Nicastrin (Nct), a transmembrane glycoprotein, is an integral component of the high molecular weight gamma-secretase complex that is responsible for cleaving the beta-amyloid precursor protein to produce amyloid beta and the intracellular domain. Nct has thus been implicated in Alzheimer's disease (AD). Currently, there is no report on the role of Nct in the embryonic development of zebrafish. We sought to validate that mutant *hi1384* from previous retroviral insertion screen is due to a mutation in the zebrafish *nct* gene and analyze its mutant phenotype. RT-PCR data supported our morpholino (MO) and mutant analyses. Furthermore, we were able to partially rescue its phenotype using the full length *nct* mRNA. These data confirm that *hi1384*$^{-/-}$ is deficient in *nct* gene. Notably, our microarray data between zebrafish *nct*^{hi1384} mutant and wild-type showed highly dynamic transcriptional profile of genes associated with studies in AD. Differential expressed genes of the *nct*$^{-/-}$ were subjected to Ingenuity Pathway Analysis (IPA) to identify the genes specific to various functional groups and pathways. Apoptotic genes were also discovered during transcriptome analysis. Since *caspase 3* is one of the downregulated genes, we examined related genes such as *acinus* and found that Nct is required for neuronal development in the mid- and hindbrain of zebrafish. The results of these analyses indicate that zebrafish *nct* $^{-/-}$ could potentially be used as an animal model for the study of AD.

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